PATENT COOPERATION TREATY

PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 33482-00/PCT | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/13156 | 12/05/2000 | 13/05/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K39/39 | | |
| Applicant<br>AMERICAN CYANAMID COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 05/12/2000 | 12.07.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Bigot-Maucher, C<br>Telephone No. +49 89 2399 7415 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/13156

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-105 as originally filed

**Claims, No.:**

1-87 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**II. Priority**

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-17 and 62-87 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 11-17 and 62-87 relate to the following subject matter which does not require an international preliminary examination (*specify*):
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 16, 20, 29-31, 40-42, 64-65, 68-81 |
| | No: | Claims | 1-15, 17-19, 21-28, 32-39, 43-63, 66-67, 82-87 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 16, 20, 29-31, 40-42, 64-65, 68-81 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 18-61 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

Preamble:

The invention relates to antigenic compositions comprising (1) a particular monophosphoryl lipid A, (2) a cytokine, lymphokine, its agonist or antagonist and (3) one particular antigen derivable from different organisms or cells as well as to methods using said compositions.

Item II:

The **priority of claims 1-87 is not valid** for the following subject-matter, since the following technical features could not be found in the priority document:

| | |
|---|---|
| - claim 1: | "allergen", "amyloid peptide protein", (1)... and "analogs thereof" |
| - claim 16: | "allergic response" |
| - claim 17: | "amyloid deposition" |
| - claims 20, 65, 69: | sequence ID NO 2 |
| - claims 29-31, 70-75: | subject-matter related to "SIV" |
| - claims 42, 78: | "porin B protein" |
| - claims 53, 84, 87: | "fusion (F) protein" |

Thus, the intermediate documents "WO-A-99 40937" (D9) and "WO-A-99 27944" (D8) published between the priority date and the filing date are considered to be state of the art for the afore-mentioned parts of the application without a valid claim to priority and therefore taken into account for the examination of novelty and inventive step.

Item III:

Claims 11-17 and 62-87 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Item V:

Reference is made to the following documents:

D1: WO-A-98 57659
D2: WO-A-99 12565
D3: WO-A-95 29700; cited in the application
D4: WO-A-98 56415
D5: WO-A-97 28273
D6: WO-A-99 02132
D7: VACCINE,
vol. 12, no. 12, 1994, pages 1132-1140
D8: WO-A-99 27944

1. Articles 33(2) and 33(3) PCT

1.1. **Independent claim 1 does not appear to be novel** (Article 33(2) PCT) in the light of D1 or D8 (D8 is relevant for antigenic compositions comprising antigens from an allergen or from an amyloid peptide protein; see Item II herein above).

D1 discloses a vaccine comprising an adjuvant and an antigen from HIV-1, RSV, bacterial pathogens, parasites etc (p 4, l 17 to p 5, l 30). Said composition also comprises 3-O-deacylated monophosphoryl lipid A (3D-MPL) (p 6, l 17-19) and a cytokine (claim 1).

D8 relates to compositions comprising the amyloid Aß peptide and monophosphoryl lipid or 3D-MPL (claims 1, 2 and 4; p 26, l 17) and a cytokine as adjuvant (p 27, l 10-14) or as carrier (p 20, l 8) to induce an immunogenic response against Aß.

1.2. The same applies to the following dependent claims, as they only contain additional technical features which are also disclosed in D1 or D8:
- **claim 2**:

D1, p 4, last lines; D8, abstract
- **claims 4-5, 7, 22-23, 25, 33-34, 36, 44-45, 47, 55-56, 58**:
D1, claim 1; D8, p 20, l 8-9
- **claims 9, 27, 38, 49, 60**:
D1, p 6, l 1-2; D8, p 20, l 33-34
- **claims 18-19**:
D1, p 4, l 22 and claim 1
- **claims 51-53**:
D1, p 4, last lines

1.3. The subject-matter of **dependent claims 40-42, 78 and 81 is novel** in the light of D1, since it is distinguished therefrom in that porin B protein of Neisseria gonorrhoeae is the used antigen.

**Claims 40-42, 78 and 81 are however not considered inventive** in the light of D1 and D5, since D5 discloses the use of porin B protein antigen for vaccines (abstract) against Neisseria gonorrhoeae (p 5, l 29 to p 6, l 4).

1.4. **The subject-matter of dependent claims 20, 64-65 and 68-69 appears to be novel** in the light of the closest prior art D1, since it is distinguished therefrom in that the specific sequences are claimed.

**The subject-matter of dependent claims 20, 64-65 and 68-69 does however not appear to be inventive** in the light of D1 and D3, since the claimed sequences are known from D3 as synthetic HIV antigens useful for the induction of antibody production (see claims 1-2 and table III, T1-SP1(A) and table XXIII, T1-SP10MN(A) identical with sequence ID NO 1; table XXVI, C4-V3 MN identical with sequence ID NO 2).

1.5. **The subject-matter of dependent claims 3, 6, 8, 10, 21, 24, 26, 28, 32, 35, 37, 39, 43, 46, 48, 50, 54, 57, 59 and 61 is not considered novel** for those parts of the invention not having a valid claim to priority (see Item II above), since D8, p 25, l 37 to p 26, l 1, discloses 3-O-deacylated monophosphoryl lipid A in combination with a stable oil-in-water emulsion.

**For the parts of the invention having a valid priority, claims 3, 6, 8, 10, 21, 24, 26, 28, 32, 35, 37, 39, 43, 46, 48, 50, 54, 57, 59 and 61 are considered novel**, since D1, which is considered the closest prior art, describes only the use of 3-O-deacylated monophosphoryl lipid A without specifying a particular state of it.

**However, the subject-matter of dependent claims 3, 6, 8, 10, 21, 24, 26, 28, 32, 35, 37, 39, 43, 46, 48, 50, 54, 57, 59 and 61 does not appear to be inventive** (Article 33(3) PCT) in the light of D1, since no surprising technical effect seems to arise from the fact that the lipid A is used in the form of a stable oil-in-water emulsion.

1.6. The subject-matter of **independent claims 11-12 is not considered novel** in the light of D1, p 4, 4th par and p 1, l 1, which also discloses a method for stimulating an immune response using an antigenic composition containing an antigen such as from a virus for instance.

1.7. The subject-matter of independent claims 13-14 only differs from claims 11-12 in that it is specified that cytotoxic T lymphocytes are to be elicited. Said additional technical feature is also disclosed in D1 (p 1, l 25 for instance). Thus, **independent claims 13-14 do not appear to be novel** in the light of D1.

1.8. Independent claim 15 differs from independent claims 11-14 in that a therapeutic or prophylactic anti-cancer effect is to be elicited. Since said additional technical feature is already disclosed in claim 6 of D1, the subject-matter of **independent claim 15 is not considered novel** in the light of D1.

1.9. The subject-matter of **independent claim 16 appears to be novel** in the light of D2, since a cytokine, lymphokine, an agonist or an antagonist is additionally comprised in the composition.

D2 describes a oil in water emulsion comprising 3D-MPL (claim 9) and an antigen selected from HIV proteins (claim 11) or allergens (p 10, l 13-15) for instance.

Thus, the technical problem to be solved in view of D2 appears to be the provision of an antigenic composition which induces an enhanced immune response in a host.

The problem is solved as disclosed above.

Said solution does not appear to be inventive in the light of the combined teaching of D1 and D2, since D1 discloses the use of a cytokine in such a composition for enhancing the immune response (see D1, p 10, l 22-23). It is considered obvious to provide the compositions with the different kinds of antigens from D2 with a cytokine as it is done in D1. Therefore, **independent claim 16 is not considered to meet the requirements of Article 33(3) PCT.**

1.10. The subject-matter of **independent claim 17 does not appear to be novel** in the light of D8 (see Item II). D8 already discloses a method of preventing or treating a disease characterized by amyloid deposit in a patient (claim 8). Said treatment includes administering a composition comprising an agent effective to induce an immune response against a peptide component of an amyloid deposit in a patient wherein the agent comprises Aß peptide (claim 16) and MPL as an adjuvant (claim 38). The pharmaceutical composition may include other adjuvants (p 28, l 14-15). Other adjuvants include cytokines (p 27, l 10-14) (see also summary under 1.1. herein above).

1.11. The subject-matter of independent claims 62-63 differs from independent claims 11-12 in that "HIV antigen" is specified. Since HIV as antigen is already disclosed in D1 (p 4, l 22), **independent claims 62-63 do not appear to be novel** in the light of said document.

1.12. **The subject-matter of independent claims 66-67 does not appear to be novel** in analogy to claims 13-14 (see 1.3. herein above).

1.13. **Independent claims 70-71, 73-74**, which differ from independent claims 11-12 and 13-14 in that "SIV antigen" is specified, as well as **dependent claims 29-31, 72 and 75 are considered novel**, since they are distinguished from

D1 in that the feature "SIV antigen" is disclosed.

The subject-matter of claims 70-71, 73-74 and 29-30 does not appear to be inventive in the light of the combined teaching of D1 and D6.
D6 discloses an oil-in-water emulsion for vaccination comprising a nucleic acid encoding HIV or SIV antigen (p 14, l 15ff and especially l 30-31), monophosphoryl lipid A (p 33, l 35) and a cytokine (p 34, l 30) for instance.

D1 already discloses the possibility to use the HIV peptide instead of the nucleic acid encoding it in a composition comprising monophosphoryl lipid A and a cytokine (see summary under 1.1.).

The skilled person, looking for an alternative vaccine composition, and being aware of D6 and D1, would be prompted to use the SIV peptide (see also D7, p 1138, 1st col, 2nd par) instead of the nucleic acid encoding it.

**Thus, the subject-matter of independent claims 70-71, 73-74 and dependent claims 29-30 are not considered inventive** according to Article 33(3) PCT.

**The subject-matter of dependent claims 31, 72 and 75 does not appear to be inventive**, since the additional technical feature does not seem to lead to a surprising effect.

1.14. **The subject-matter of independent claims 76-77 and 79-80 is novel, but not inventive** in the light of the combined teaching of D1 and D5 for the same reasons as dependent claims 40-42, 78 and 81 (see 1.3. herein above).

1.15. **The subject-matter of independent claims 82-83 does not appear to be novel** in the light of D1, since D1 (p 4, l 17 to p 5, l 1 and p 1, l 1) discloses already a method for stimulating an immune response using an antigenic composition comprising RSV.

The same applies to **dependent claims 84 and 87** (see D1, p 4, last lines).

1.16. **The subject-matter of independent claims 85-86 does not appear to be novel** in analogy to claims 13-14 (see **1.3.** herein above).

2. Industrial Applicability

For the assessment of the present claims 11-17 and 62-87 on the question whether they are industrially applicable, no unified criteria exist in the PCT contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. The subject-matter of the interfering document "WO-A-99 27944" (D8) refers to relevant subject-matter.

The above document is published after the present application's priority date, but before its filing date and is therefore relevant for those parts of the present application, if any, which do not have a valid claim to priority (see Item II above).

4. It should be noted that the compositions comprising the different substances (see preamble herein above) and their use are well-known in the art (see Item V, 1 and D1, D8). Therefore, the following groups of claims relating to different antigens do not seem to be so linked as to relate to a single general inventive concept:

- antigen from a pathogenic virus (claims 1-14 partially)
- antigen from a bacterium (claims 1-14 partially)
- antigen from a fungus (claims 1-14 partially)
- antigen from a parasite (claims 1-14 partially)
- antigen from a cancer cell or tumor cell (claims 1-10 partially and claim 15)
- antigen from an allergen (claims 1-10 partially and claim 16)
- antigen from an amyloid peptide (claims 1-10 partially and claim 17)

- antigen from HIV (claims 1-10 partially and claims 18-28, 62-69)
- antigen from SIV (claims 1-10 partially and claims 29-39, 70-75)
- antigen from Neisseria gonorrhoeae (claims 1-10 partially and claims 40-50, 76-81)
- antigen from RSV (claims 1-10 partially and claims 51-61, 82-87).

If the applicant wishes to proceed to the national phase before the EPO, an objection against these claims because of lack of unity will have to be awaited.

Item VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 and D4-D8 is not mentioned in the description, nor are these documents identified therein.

Item VIII:

Lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1-87 do not meet the requirements of Article 6 PCT.